How to handle non-linearity in absorption: a case study in oncology

Sophie Peigné[1], Donato Teutonico[1] and Marylore Chenel[1]
[1]Clinical Pharmacokinetics and Pharmacometrics division, Servier, France

Context

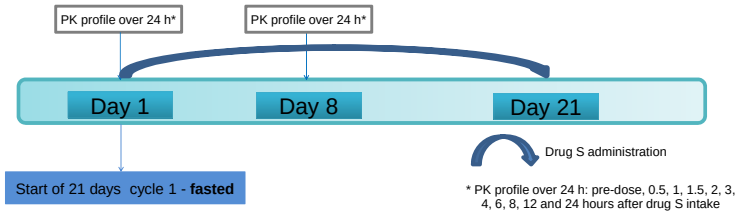
Drug S is an orally administered compound with a complex absorption due to a low solubility, currently in clinical development for cancer therapy. Two dose escalation phase I clinical studies with drug S taken once per day, without food, during a 21 days cycle, are ongoing to determine the safety profile and the tolerability of this drug. In addition, the influence of food intake was assessed in a cohort of one of the 2 clinical studies after single oral administration of drug S.

Objectives

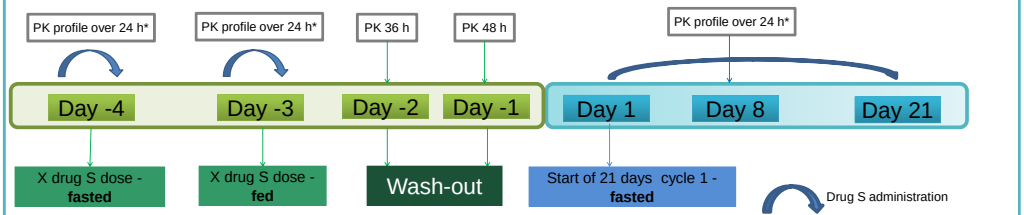
To assess the pharmacokinetic (PK) of this drug in patients, to investigate potential non-linearity, to quantify the variability in patients, to identify such variability and *in fine* to help for the dose selection in phase II.

Study design & PK samples

- **Studies 1 & 2**



- **Food interaction cohort**



Methods

- Population modelling approach using MONOLIX version 4.3
- Several absorption models and different elimination processes (*i.e.* linear or non-linear elimination) were tested
- Covariate analysis: impact of demographic characteristics as well as food effect
- Due to the solubility issues of this compound, dose effect tested on absorption parameters

Results

- **PK Data: large inter individual variability**

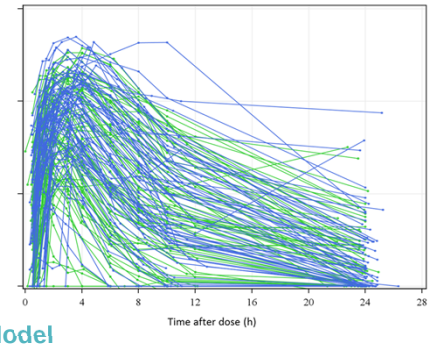


Figure 1 - Spaghetti plot
Day1 - **Day8**

- **Model**

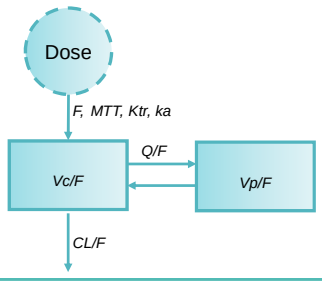


Figure 2 - Basic PK model
F: bioavailability
Ktr: transit rate constant
MTT: mean transit time
ka: 1st order absorption rate constant
Vc/F: central volume of distribution
Vp/F: peripheral volume of distribution
Q/F: intercompartmental clearance
CL/F: elimination clearance

- **Dose effect on MTT & Ktr parameters**
  - Impact: longer absorption for the higher doses
  - Possible explanation: solubility issues with the increasing number of tablets administered with dose increasing
- **Food effect**
  - Impact: food intake increased the bioavailability by a 6 fold factor and the MTT parameter by a 3 fold factor
- **Model evaluation: Good description of the data**

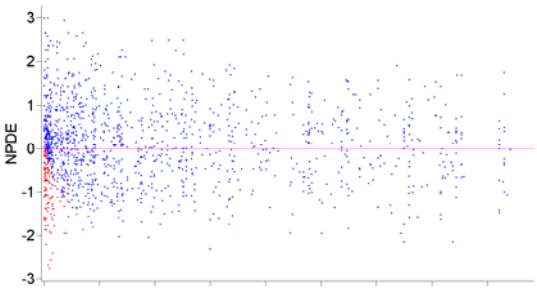


Figure 3 – Normalized Prediction Distribution Error (NPDE) vs population predictions

Conclusion

The current developed model allowed a good description of the PK data for the drug S. The non-linearity in absorption, handled using a dose effect on absorption parameters, could be related to the solubility and the number of dosage forms administered. As soon as PD data will be available, they will be included to build a PK/PD model. This model will help for the dose selection in phase II.

MID3 value: low impact as description of data, nevertheless high added value as allow better understanding of drug S PK. [1]

[1] EFPIA MID3 Workgroup et al. CPT Pharmacometrics Syst Pharmacol (2016)